

### **REMARKS**

Reconsideration of the various objections and rejections is respectfully requested, in view of the following remarks.

#### **Status of the Claims**

Claims 1, 3-4 and 6-18 are pending.

#### **Amendment to the Claims**

The claims are amended to more particularly set forth that which Applicants consider to be their invention. Support for the claim amendments is as follows. In claim 1, the elements, "synthetic" and "wherein the synthetic bidirectional promoter is endogenously regulated," are supported, e.g., by the specification at page 23, lines 16-19.

Claim 4 is amended to include the elements of claim 5, and claim 5 is newly cancelled, without prejudice.

Claims 2 and 14 are also amended to conform articles to U.S. usage.

It is submitted that no new matter has been added.

#### **The Claims Are Novel Over Chtarto Under 35 U.S.C. § 102(e)**

Claims 1, 3-4 and 6-15 have been rejected as allegedly anticipated by Chtarto et al. ("Chtarto;" US 6,780,639) under 35 U.S.C. § 102(e). Beginning at page 4 of the Office Action, the Examiner takes the position that Chtarto discloses "expression vectors . . . comprising a bi-directional promoters . . . comprising two minimal CMV promoters oriented in opposite

directions, as well as insertion sites for foreign sequences," etc. The Examiner has maintained this rejection in the Advisory Action.

Applicants respectfully disagree. The Examiner's attention is respectfully directed to the above provided amendments to the claims, and to the enclosed Declaration of Luigi Naldini Under 37 C.F.R. § 1.132 ("the Declaration"). Claim 1 requires that the subject bidirectional promoter be "synthetic" and also requires that the subject synthetic bidirectional promoter is "endogenously regulated." As explained by the Declaration, at ¶ 4, the bidirection promoter taught by Chtarto is based only on a prokariotic Tet responsive system. Nowhere does Chtarto teach or suggest that the subject bidirectional synthetic promoter include, "a promoter sequence of an animal gene comprising an enhancer region and a second minimal promoter sequence..." Further, nowhere does Chtarto teach or suggest that the subject bidirectional synthetic promoter be endogenously regulated. In fact, the Chtarto promoter must, by its construction, be exogenously regulated. This is clear because Chtarto teaches that their promoter includes a Tet element that is regulated by exogenously provide tetracycline. This is also clearly explained by the instant specification, as follows.

Inducible bi-directional promoters were originally developed in Tet-regulated expression systems, by duplicating a minimal promoter on both sides of a series of Tet operator repeats, to obtain exogenously regulated expression of two transgenes<sup>36, 40, 41</sup>. This design was recently applied to other systems that also combine prokaryotic enhancer elements with chimeric trans-activators to regulate gene expression. Although these inducible expression systems represent powerful tools for gene-function studies, they are dependent on co-expression and functional activity of protein trans-activators, and pose several challenges when applied to vector-based delivery and in vivo applications

Page 23, lines 7-15 (Underline "\_\_\_" added for emphasis). The above-quoted explanation from the specification is submitted to explain the shortcomings of Chtarto as an anticipating reference, and to explain the shortcomings of the remaining art of record.

For all of these reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

**The Claims Are Novel Over Itoh Under 35 U.S.C. § 102(e)**

Claims 1, 3-4 and 6-11 and 13-18 have been rejected as allegedly anticipated by Itoh et al. ("Itoh;" US 6,995,011) under 35 U.S.C. § 102(e). Beginning at page 7 of the Office Action, the Examiner takes the position that Itoh teaches, "retroviral expression vectors comprising a bi-directional promoter comprising two minimal CMV promoters (Tet responsive promoter) oriented in opposite directions as well as insertion sites for foreign sequences, polyadenylation sites downstream of the insertion sites and at least one IRES element." The Examiner has maintained this rejection in the Advisory Action.

Applicants respectfully disagree. As noted above, claim 1 requires that the subject bidirectional promoter be "endogenously regulated." As attested to by the Declaration, at ¶¶ 5-6, Itoh teaches a bidirectional promoter that is regulated by means of exogenously administered compounds, e.g., at the Tet-responsive promoter. In addition, Itoh fails to teach or suggest the requirement of claim 1 that, "the two promoter sequences driving a coordinate transcription of said coding sequences in the opposite orientation," and that this operate, "in animal cells," as attested to by the Declaration at ¶6.

For all of these reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

**The Claims Are Novel Over Fux Under 35 U.S.C. § 102(b)**

Claims 1-4, 7-8, 10 and 14 have been rejected as allegedly anticipated by Fux et al., *Biotechnol. Prog.* 2003, 19, 109-120 ("Fux"). Beginning at page 9 of the Office Action, the

Examiner takes the position that, "Fux et al. (cited by applicants, see whole article, particularly the paragraph bridging pp. 109-110, Table 1, Fig. 1, p. 114) teach bidirectional expression cassette systems comprising a minimal CMV promoter and a promoter derived from an animal gene (can be a minimal promoter) and a method for expression of multiple genes in animal (can be human) cells." The Examiner has maintained this rejection in the Advisory Action.

Applicants respectfully disagree. Claim 1 requires, *inter alia*, that the "the two promoter sequences" of the subject synthetic bidirectional promoter," are "driving a coordinate transcription of said coding sequences in the opposite orientation." Fux describes plasmids carrying two completely independent promoters, each with different activity and inducibility. Thus, it is clear that Fux fails to teach or suggest the coordinate transcription of coding sequence in the opposite direction, that is required by the instantly claimed invention (Declaration ¶7). Fux describes efficient dual regulated promoters (Declaration ¶8). Fux describes insertion of noncoding stuffer fragments or chicken HS4 (cHS4) insulators to minimize interference between the two provided promoters (Declaration ¶8), which confirms this conclusion.

Further, the PIT- or tTA-specific operators mentioned by Fux (pir; tetO) are synthetic sequences derived from prokariotic sources, and cannot be regarded as endogenously regulated enhancer regions (Declaration ¶9).

For all of these reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

**Claim 5 is Nonobvious Under 35 U.S.C. § 103(a)**

Claim 5 has been rejected as allegedly obvious over Chtarto (as above) or Itoh (as above), either in view of Hope et al. ("Hope;" US 6,136,597). Beginning at page 12 of the Office Action, the Examiner takes the position that,

The ordinary skilled artisan, seeking to increase expression of a transgene, in cells transduced with a bi-directional expression vector system would have been motivated to combine the teachings of Chtarto et al. or Itoh et al. on the generation of expression vectors with bi-directional promoters with the teachings of Hope et al. on inclusion of WPRE elements in expression systems because Hope et al. teaches that inclusion of post-transcriptional elements such as WPRES increases the expression of transgenes contained in the vectors.

The Examiner has maintained this rejection in the Advisory Action.

Applicants respectfully disagree. Claim 5 is cancelled, thus obviating this rejection. In addition, the elements of claim 5 are now included in claim 4, which depends from claim 1. The failings of Chtarto and/or Itoh as prior art against the instantly claimed invention of e.g., claim 1, are detailed *supra* and further explained by the Declaration at ¶10. Given the failings of Chtarto and/or Itoh, in any combination with Hope, the artisan would not have been able to achieve the invention as recited by claim 4. Neither Chtarto and/or Itoh teach or suggest a inclusion of a post-transcriptional regulatory element positioned upstream to one or both of the poly A sites. Hope certainly would not have remedied these clear deficiencies. Adding the teachings of Hope to the combination of Chtarto and/or Itoh, taken in any combination, will only result in a divalent promoter that fails to correspond to what is required by claim 1, and therefore, fails to render obvious the invention of claim 4.

For the above reasons, it is submitted that the Patent Office has failed to meet the required burden for maintaining a *prima facie* rejection of claim 4. Nevertheless, if the Examiner maintains the rejection, Applicants also submit that the invention of claim 4 represents a long sought improvement in the art. This confirmed by the substantial number of references,

(seventy-eight) that cite the article (Amendola et al., 2005, *Nature Biotechnology* 23(1): 108-116) reporting the work exemplifying the instantly claimed invention (copy enclosed as **Exhibit A**). Confirming this citation history, Applicants also enclose herewith a printout of a citation index search, attached to this Response as **Exhibit B**. This is offered as secondary evidence of nonobviousness, as held by the Supreme Court in *Graham v. John Deere Co.* (383 U.S. 1, 148 USPQ 459 (1966)).

For all of these reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

### **Conclusion**

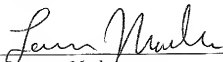
This Response is being filed with 1 independent claim and 16 total claims. Thus, no fee is believed to be owed for entry of this Response. If, on the other hand, it is determined that further fees are necessary or any overpayment has been made, the Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

This Response is being filed with a petition for an extension of time for three months, together with the required fee for a small entity. Pursuant to 37 CFR 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to the above-mentioned deposit account.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

LUCAS & MERCANTI, LLP

By:   
Laurence Manbet  
Registration No. 35,597

LUCAS & MERCANTI, LLP  
475 Park Avenue South  
New York, NY 10016  
212-661-8000  
212-661-8002

MNM/LM